REMARKS

Reconsideration of the Examiner's rejection of the present application is requested respectfully in view of the above amendments and the following remarks.

STATUS OF THE CLAIMS

Claims 1-12 were pending at the time of the present Office Action. Claims 8-12 stand withdrawn from consideration as non-elected under a restriction requirement. Claims 1, 4, 5 and 7 have been amended. Withdrawn claims 8, 11 and 12 have also been amended. No claims have been added or deleted. No new matter has been added by these amendments. Therefore, claims 1-7 are now presented for review.

SUMMARY OF OFFICE ACTION

The Restriction Requirement previously presented has been made final.

Claim 7 stands rejected under 35 U.S.C. §112, first paragraph, as not being enabling for prophylaxis.

Claims 1-7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brendel et al. US 6,531,495 (Brendel '495) in view of Smith et al. US Pub. No. 2002/0161018 (Smith).

THE RESTRICTION REQUIREMENT

In accordance with the restriction requirement, applicant elected to proceed with the composition claims of Group I, claims 1-7. The claims of Group II, claims 8-12, are directed to methods of using the compositions of Group I. In order to preserve the right to rejoin the method claims of Group II once allowable subject matter has been identified in the claims of Group I, amendments have been made to withdrawn claims 8, 11 and 12 to maintain their consistency with amendments made to the claims of Group I.

If claims 1-7 are found allowable in view of this response, rejoinder of claims 8-12 is respectfully requested.

Also in accordance with the election under the restriction requirement, applicants elected to proceed with compounds of the formula Ib as shown in claim 1. Formula Ia has been deleted, and compositions including compounds of formula Ia have also been deleted.

It is submitted that the amended claims are all within the scope of the election under the Restriction Requirement. Applicant reserves the right to pursue non-elected subject matter in subsequent application(s).

THE REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claim 7 stands rejected under 35 U.S.C. §112, first paragraph, as not being enabled for use of the term "prophylaxis" in the phrase "therapy or prophylaxis". Applicant has deleted the phrase "therapy or prophylaxis" from claim 7 (as well as withdrawn claim 8) to render the present rejection moot. Instead, applicant has substituted the word "treatment" in these claims. This word finds support throughout the specification. For example, paragraph 1 on page 5 speaks of the use of the claimed compositions for the treatment of supraventricular arrhythmias such as atrial fibrillation or flutters. Similarly, the second full paragraph on page 19 discusses the use of the claimed compositions for the treatment of atrial fibrillation or atrial flutters. The term "treatment" is used throughout the specification with reference to the administration of the claimed compositions, and details of the dosages, dosage forms, excipients and other enabling support are also provided throughout the specification, particularly at pages 19-21. Clearly the specification is fully enabling for the treatment of these medical conditions by the administration of the presently claimed composition.

THE REJECTION UNDER 35 U.S.C. §103

Claims 1-7 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Brendel '495 in view of Smith. Applicants respectfully traverse this rejection.

As the Examiner indicates, the compounds of formula Ib as set forth in claim 1 are disclosed in Brendel '495, which is in fact an earlier patent with a joint inventor of the present application, and the compound of present Example 1 is disclosed in Brendel '495. Claim 15 of Brendel '495 does indicate that such compounds can be combined with IK_r channel blockers. Smith does teach that ibutilide is a known IK_r channel blocker. However, there is no teaching in the Brendel '495 patent (or Smith) that the combination of the biphenyl compounds of formula Ib, as exemplified by present Example 1, would have the superadditive effect when used with IK_r channel blockers, as taught and demonstrated in the present application. It is for this reason

that the combination claimed in the claims of the present application are patentably distinct from the teaching of Brendel '495.

The experimental procedures and test results regarding the presently claimed combinations of drugs are explained in the specification, particularly on pages 28 to 40. As set forth beginning on page 29, one measure used to evaluate the atrial effectiveness of such compounds is the atrial effective refractory period (AERP), discussed in detail in the specification. AERP values were measured on normal animals, and on animals in which atrial fibrillation was induced, referred to as electrical remodeling. Such electrical remodeling is believed to simulate the effect of a patient who has gone through atrial fibrillation, and such patients would be considered prospective users of the presently claimed compositions.

Table 1 on page 31 presents the results of tests conducted using the compound of Example 1 in combination with the IK_r channel blocker ibutilide. The first line has the results for non-remodeled normal animals, and the second line the results for animals that were subjected to electrical remodeling. In each case the results show ibutilide alone vs. a first control, and then Ex. 1 alone vs. a second control, as well as the combination of Ex. 1 and ibutilide vs. the second control. The effectiveness of the compounds are determined by comparing the differences between the control values and the treated values. The results, discussed in detail on page 30, show an additive effect of combining the two drugs on non-remodeled animals, but a super-additive effect on electrically remodeled animals. On the remodeled animals, the effect of ibutilide by itself was only about 5 ms, but that of Ex. 1 was about 63 ms. Yet, when the ibutilide was combined with Ex. 1, the difference was about 94 ms. This shows a surprisingly large improvement by combining ibutilide with Ex. 1, that would not be predicted from the minimal effect of ibutilide by itself on such remodeled animals.

In like manner, Table 2 on page 32 presents corresponding test results on the use of Ex. 1 with the IK_r channel blocker dofetilide. These results are discussed on pages 31-32. Again, on non-remodeled animals the combination of Ex. 1 and dofetilide is roughly additive. However, in the tests on remodeled animals the tests yield super-additive results. Dofetilide by itself increases the AERP by only 7 ms. But in combination with Ex. 1, dofetilide increases the AERP value of Ex. 1 by about 20 ms. This super-additive increase in AERP could not have been predicted from a reading of Brendel '495.

As summarized on page 33, the positive effect on AERP with the administration of the IK_r channel blockers ibutilide or dofetilide is markedly lower in the remodeled atrium as opposed to the normal atrium. Yet, when these IK_r channel blockers are administered in combination with Ex. 1 to remodel animals, they produce a much greater increase in the AERP values than would have been predicted. It is this super-additive effect which clearly demonstrates the unexpected synergism of combing IK_r channel blockers with compounds of Formula Ib as exemplified by Example 1.

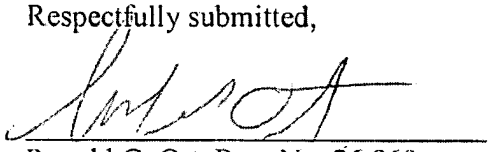
A separate study presented on pages 33-40 of the specification is directed to the effect of the claimed combination of drugs on the cardioversion in chronically fibrillating test animals. The details of the test procedures and results are set forth in the specification. The results presented in Table 5 on page 40 show the improvement obtained by combining the compound of Example 1 with ibutilide or dofetilide. Again, these results show the surprising super-additive effect of combining these components. The first line of Table 5 shows the effect of ibutilide or dofetilide alone, that is with 0 mg/kg of Ex. 1. The remaining lines show the increase in effectiveness achieved by combining ibutilide or dofetilide with different dosages of Ex. 1. In general, these increases are more than would be predicted from the results in line 1 for these IK_r channel blockers without Ex.1.

It is therefore submitted that the test results presented in the specification clearly demonstrate the unexpected synergism obtained by combining an IK_r channel blocker with a compound of Formula Ib as claimed in claim 1. Thus the present invention would not have been obvious from a reading of Brendel '495, with or without Smith. The Examiner is respectfully requested to reconsider and withdraw the present rejection under 35 U.S.C. §103(a) in view of the above.

It is submitted that the claims in the present application are now in condition for allowance, and action to that effect is respectfully requested.

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this Amendment to Deposit Account 18-1982.

Respectfully submitted,



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